REVIEW 10.1111/j.1469-0691.2004.01020.x

Effects of varicella vaccination on herpes zoster incidence

S. Wagenpfeil[1], *A. Neiss*[1] *and P. Wutzler*[2]

[1]Institute for Medical Statistics and Epidemiology, Technical University of Munich, Munich and [2]Institute for Virology and Antiviral Therapy, University of Jena, Jena, Germany

ABSTRACT

The effects of a general varicella vaccination programme on the incidence of herpes zoster are of major public health importance. This review focuses on two key aspects, namely the relationship between wild-type virus spread and the incidence of herpes zoster, as obtained from recent surveys, surveillance and observational studies, and the results from mathematical population models. Although knowledge is limited, close contact with varicella cases seems to have a protective effect. Thus, an increase in zoster incidence after varicella immunisation is possible, but the extent is unknown because of the influence of other factors independent of immunisation. Currently, vaccination effects estimated from mathematical modelling depend strongly on pre-specified assumptions. In order to obtain more precise predictions, the results of ongoing monitoring and clinical studies are awaited and further studies are suggested. Vaccination recommendations can be adapted at any time to take account of further findings in this area.

Keywords Chickenpox, population models, review, shingles, vaccination, varicella zoster virus

Accepted: 6 July 2004

Clin Microbiol Infect 2004; 10: 954–960

INTRODUCTION

A general varicella (i.e., chickenpox) vaccination programme for all children aged 12–18 months, and further catch-up strategies, were introduced in the USA in 1996 [1]. No empirical baseline data were available at that time regarding the impact of a universal vaccination programme on varicella epidemiology. Concerns have been raised about a potential age-shift, i.e., an increase in the absolute number of diagnosed varicella cases in older age groups, in which varicella generally results in a more severe disease course. Although the relative number may increase, Klose *et al.* [2] and Banz *et al.* [3] found no evidence indicating an age-shift in primary varicella infection with immunisation levels of >50%. However, this may occur with immunisation levels of <50% [3], which is a similar degree of coverage to that reported by Panagiotopoulos *et al.* [4] for rubella vaccination in Greece. Nevertheless, since the introduction of universal varicella vaccination in the USA, no general age-shift in varicella cases has been observed to date [5].

A further concern is the potential initial increase in herpes zoster incidence resulting from a decrease in the spread of wild-type varicella zoster virus (VZV) following vaccination. The reasoning behind this is that virus shed from varicella cases may inhibit reactivation of latent virus, and thus protect latent-infected individuals from developing herpes zoster. However, the exact mechanism of reactivation is not known. Three possible pathways should be considered, in that virus shed from an infectious varicella case either may or may not stimulate, or may inhibit, the reactivation of latent virus [6]. Additional factors such as ageing and immunocompetence should also be taken into account.

Currently discussed risk factors for herpes zoster have been summarised by Thomas and Hall [7]. In order to determine the possible effects of vaccination on the incidence of herpes zoster, it is essential to know how much VZV reactivation is caused by factors influenced by vaccination, such as virus shedding, and how much is caused by other factors uninfluenced by vaccination. The issue is of major public health importance, both in

Corresponding author and reprint requests: S. Wagenpfeil, Institute for Medical Statistics and Epidemiology, Klinikum rechts der Isar der TU München, Ismaninger Strasse 22, D-81675 Munich, Germany
E-mail: Stefan.Wagenpfeil@imse.med.tu-muenchen.de

countries that have already implemented a general vaccination programme against varicella, and in countries that are currently debating the implementation of such a programme.

This review describes empirical and analytical methods for addressing two essential questions: (1) what is the relationship between wild-type virus spread and incidence of herpes zoster; and (2) what is the influence of a general varicella vaccination programme on herpes zoster incidence? Factors influencing the reactivation of VZV are discussed, as well as the potential risks of reactivation following vaccination. An overall keyword search in MEDLINE yielded 240 international publications in the years 1990–2004. When keywords were restricted to the title, only 18 publications were found. In addition to an essential paper from 1992 [6], Tables 1–3 give an overview of the work reviewed and the issues addressed in publications since 2000.

EMPIRICAL METHODS

The methods of investigation used in the studies can be divided into two different groups: statistical analysis of empirical data from the pre-vaccination and post-vaccination eras, and mathematical modelling of disease courses with simulation techniques in analytical approaches.

Empirical data come mainly from England, Wales, Canada and the USA in the form of surveys and case reports. However, it is only possible to make pre- and post-vaccination comparisons with data from the USA. In other countries with no general varicella vaccination programme, the influence of surrogates for virus shedding and varicella contacts on herpes zoster incidence is determined with odds ratios and time-series analyses.

Various groups have studied hospital admission data to determine the baseline relationship between varicella and herpes zoster incidence in the pre-vaccination era [8,9]. An extensive Kaiser Permanente Medical Care Program (KPMCP) in Oakland, CA, USA was launched to specifically evaluate a possible age-shift in future varicella cases and to monitor the incidence of herpes zoster [10]. Interim 6-year data from the KPMCP study refer to herpes zoster hospitalisation rates pre- and post-vaccination [11]. Gershon [5] reported varicella and herpes zoster surveillance data and described the current situation in the USA. Data were from the medical records of a Health Maintenance Organization in Seattle and a statewide survey from Massachusetts. These studies provided the first empirical data from the USA, a country with an ongoing universal vaccination programme. Goldman [12] reported the first findings from active surveillance in Antelope Valley, USA, for the years 2000 and 2001, and the same author [13] estimated herpes zoster incidence rates before widespread vaccination by analysis of an adolescent survey in the same district. The remaining studies in Tables 1–3 are from countries without a general vaccination programme against varicella and thus are not influenced by vaccination campaigns.

ANALYTICAL METHODS

Simulation studies based on mathematical population models have been initiated to predict the possible impact of varicella vaccination on herpes zoster incidence. Mathematical modelling is

Table 1. Studies on the relationship between varicella and herpes zoster: empirical and epidemiological studies

Study/Investigation	Type	Population	Issues addressed
Ray *et al.* [11]	Database evaluation	HMO, California, USA, 1994 and 2000	Hospitalisation rates related to varicella and herpes zoster for 1994 (pre-licensure) and 2000 (post-licensure)
Gershon [5]	Survey, medical records	USA	Varicella and herpes zoster surveillance
Goldman [12]	Surveillance	Antelope Valley, California, USA, 2000 and 2001	Ascertainment-adjusted herpes zoster incidence rates for children aged <10 years and individuals aged 10–19 years in the post-vaccination era
Goldman [13]	Adolescent survey	Antelope Valley, California, USA, 1987–2000	Cumulative herpes zoster incidence rate for individuals aged 10–14 years (1987–2000) and children aged < 10 years (1987–1995)
Thomas and Hall [17]	Case-control study	Reported cases from general practices in south London, Uk	Dependence of herpes zoster occurence in latently infected adults from re-exposure to wild-type varicella zoster virus and contacts with children

HMO, Health Maintenance Organization.

Table 2. Studies on the relationship between varicella and herpes zoster: mathematical modelling

Study/ Investigation	Type	Population	Issues addressed
Brisson *et al.* [18]	Simulation	Canada	Impact of varicella vaccination on varicella incidence and morbidity Impact of varicella vaccination on herpes zoster incidence according to different lengths of exposure to varicella
Edmunds and Brisson [19]	Simulation and review	Model	Impact of varicella vaccination on herpes zoster incidence for different vaccination strategies Review of published varicella transmission dynamic models

generally based on the same mathematical formalism of deterministic, age-structured, dynamic population models (described in more detail elsewhere [14,15]). However, the results can be very sensitive to some of the input parameters, and the model outcomes are therefore supplied with more or less extensive sensitivity analyses.

Brisson *et al.* [16] presented data from the Fourth National Survey of Morbidity in General Practices (MSGP4). The survey included 500 000 cases from general practices in England and Wales for the years 1991–1992. The results were analysed with a mathematical model designed to simulate varicella and herpes zoster incidences in the case of a virtual varicella vaccination programme. Special attention was given to the relationships between vaccination, wild-type virus spread protecting against herpes zoster, and a potential increase of herpes zoster cases in the initial stages of a vaccination programme.

Weekly rates of varicella and herpes zoster incidence for England and Wales from 1976 to 1987 were analysed by Garnett and Grenfell [6]. The data comprised records from 106 doctors collected by the Royal College of General Practitioners. The findings were analysed with a mathematical VZV model to examine the impact of vaccination on herpes zoster incidence. This is the only model to differentiate between the potential of wild-type virus to boost specific immunity and the potential of vaccine virus to recrudesce.

Thomas and Hall [17] carried out a case-control study in south London, UK, to estimate the relative risk of contracting herpes zoster as a consequence of exposure to wild-type varicella. As in Brisson *et al.* [16], contacts with children were used as a surrogate variable for virus shedding following exposure to wild-type varicella. Brisson *et al.* [18] simulated the impact of vaccination on herpes zoster incidence for the Canadian population, while Edmunds and Brisson [19] based their simulation on different vaccination strategies, supplemented with a review of published mathematical models for varicella transmission.

The results obtained in these studies (Tables 4 and 5) concern two key issues: (1) the relationship between wild-type virus spread and herpes zoster incidence; and (2) the influence of a general varicella vaccination programme on herpes zoster incidence.

RELATIONSHIP BETWEEN WILD-TYPE VIRUS SPREAD AND INCIDENCE OF HERPES ZOSTER

Results concerning the relationship between wild-type virus spread and incidence of herpes zoster are based mainly on medical records and case

Table 3. Studies on the relationship between varicella and herpes zoster: empirical and epidemiological studies combined with mathematical modelling

Study/Investigation	Type	Population	Issues addressed
Brisson *et al.* [16]	Survey and simulation	Cases from general practices in England and Wales 1991–1992	Age-specific incidence rates of varicella and zoster for adults living with and without children in their household Impact of varicella vaccination on herpes zoster incidence according to estimated length of exposure to varicella
Garnett and Grenfell [6]	Simulation and case reports	Cases from general practices in England and Wales 1976–1987	Dependencies of varicella and herpes zoster incidences Viral reactivation induced by varicella Impact of varicella vaccination on herpes zoster incidence and its dependence on the potency of varicella to boost specific immunity and the recrudescence of the vaccine virus

Table 4. Key results of recent studies and one earlier investigation: relationship between wild-type varicella zoster virus spread and herpes zoster incidence

Study/ Investigation	Population	Results
Brisson *et al.* [16]	Cases from general practices in England and Wales 1991–1992	The age-specific incidence of herpes zoster observed in the study is similar to that in other industrialised countries Young adults aged 20–40 years living with children aged < 16 years are significantly more exposed to varicella than those without children in their household People living with children aged <16 years are significantly protected against herpes zoster, even after correction for age, gender, ethnicity or socio-economic factors
Garnett and Grenfell [6]	Cases from general practices in England and Wales 1976–1987	There is no overall inverse correlation between varicella and herpes zoster incidence from time-series analysis There is no seasonal pattern for zoster At the same time (1980–1982) as varicella incidence increased significantly, herpes zoster incidence decreased significantly Indirect support for the hypothesis that contact with varicella reduces reactivation of latent virus
Thomas and Hall [17]	Reported cases from general practices in south London, UK	Living with children protects against herpes zoster because of increased contact with other children outside the household Contact with many children outside the household or occupational contact with ill children are associated with graded protection against herpes zoster. The strength of protection diminishes after known varicella contacts are controlled for

reports from England and Wales, which do not have a general vaccination programme against varicella. Table 4 gives an overview of the essential empirical outcomes. The results of all the studies show that living with children and close contact with varicella cases, i.e., exposure to VZV, are associated with a decreased incidence of herpes zoster. However, the strength of association varies between the studies. Thomas *et al.* [17] state that protection diminishes after known varicella contacts are controlled for. No further information regarding the functional mechanism of latent virus reactivation is supplied by these studies.

INFLUENCE OF A GENERAL VARICELLA VACCINATION PROGRAMME ON HERPES ZOSTER INCIDENCE

Results concerning the influence of a general varicella vaccination programme on herpes zoster incidence come from preliminary findings of the first observational studies in the USA and mathematical, dynamic population models. Table 5 summarises the main outcomes to date. Simulation models show that if varicella boosts immunity, herpes zoster incidence may increase after the launch of a vaccination programme in the short term, and may reach pre-vaccination levels in the mid-term. The time-frame is sensitive to the duration of immunity after exposure to varicella [16]. In the long term, there is a continuous reduction in herpes zoster incidence to far below pre-vaccination levels as the vaccinated cohort ages. Overall, the effects of a universal varicella vaccination programme on herpes zoster incidence depend heavily on the interaction between varicella disease and reactivation of latent virus, and simulations will be influenced strongly by the assumptions made in mathematical models.

FACTORS INFLUENCING REACTIVATION OF VZV

Very little is understood regarding the process of reactivation of latent VZV. It is known that, following an episode of primary varicella, VZV becomes latent and resides in the dorsal root ganglia. Herpes zoster, or shingles, occurs when latent VZV reactivates, causing recurrent disease that manifests typically as painful clusters of small, filled vesicles with a dermatomal distribution. Factors associated with recurrent disease include age, immunosuppression, varicella infection at a young age (< 18 months) and, for children, intra-uterine exposure to VZV [1,20]. A further factor suggested by Seward *et al.* [21] could be subclinical VZV reactivation, with a resulting boost in immunity and an unknown effect on herpes zoster incidence. Additional risk factors from epidemiological investigations, such as genetic susceptibility, sex, ethnicity, psychological stress and mechanical trauma, have been summarised and discussed by Thomas and Hall [7]. In studies of physicians in the USA with high and low rates of contact with varicella-infected patients [22], and of paediatricians and general practitioners in Japan [23], a reduced risk of herpes zoster was reported for paediatricians and general practitioners. However, these results should be interpreted with care, because of a low recall rate and a small sample size, respectively.

The MSGP4 data reported by Brisson *et al.* [16] showed an age-dependent increase in herpes

Table 5. Key results of recent studies and one earlier investigation: influence of a general varicella vaccination programme on herpes zoster incidence

Study/Investigation	Population	Results
Ray *et al.* [11]	HMO, California, USA, 1994 and 2000	Overall varicella-related hospitalisations were significantly reduced in 2000 Overall herpes zoster-related hospitalisations were significantly increased in 2000. Age stratification showed a significant increase in the 60+ age group, but no significant change in the younger age groups
Gershon [5]	USA	There was no age-specific increasing time trend in herpes zoster incidences from 1992 to 1999 No increase in herpes zoster incidence in the 70+ age group has been observed to date
Goldman [12]	Antelope Valley, California, USA, 2000 and 2001	Herpes zoster incidence rates from active surveillance for individuals aged 10–19 years are comparable to those in the pre-licensure era Herpes zoster incidence rates from active surveillance for children aged <10 years are higher than those from historical studies or surveys in the pre-licensure era. Comparison between surveillance data and historical studies or surveys may, however, be biased
Goldman [13]	Antelope Valley, California, USA, 1987–2000	The herpes zoster incidence rate for individuals aged 10–14 years compares favourably with that from another historical study Individuals aged 10–14 years do not seem to have been affected by increasing varicella vaccination levels to date
Brisson *et al.* [16]	Cases from general practices in England and Wales 1991–1992	The simulation model predicts that the herpes zoster incidence rate will increase for the first 20 years after elimination of varicella transmission, peaking at an incidence 51% higher than the pre-vaccination level. Then it will gradually decrease, reaching the pre-vaccination level 46 years after the introduction of vaccination. In the long term, herpes zoster incidence will continuously decrease until it is far below the pre-vaccination level
Garnett and Grenfell [6]	Cases from general practices in England and Wales 1976–1987	Simulation suggests that vaccination potentially increases herpes zoster incidence only if varicella does act to boost specific immunity, depending on the potential of the vaccine virus to recrudesce
Brisson *et al.* [18]	Canada	If exposure to varicella has no boosting effect on the incidence of herpes zoster, and seroconverted vaccinated persons do not acquire herpes zoster, then herpes zoster incidence declines as the vaccinated proportion of the population increases If there is a boosting effect, then herpes zoster incidence increases significantly in the short to medium term, depending on the duration of protection. In the long term, herpes zoster incidence will continuously decrease until it is far below the pre-vaccination level
Edmunds and Brisson [19]	Model	Determination of the long-term effects of universal varicella vaccination depends heavily on an understanding of the mechanisms for maintaining immunity against varicella and herpes zoster Targeted vaccination of susceptible adolescents and the contacts of high-risk individuals can be effective in preventing disease with minimal risk to the community. However, the main benefits of universal vaccination will not be achieved

HMO, Health Maintenance Organization.

zoster incidence for groups living in a household either with or without children. This finding is in agreement with current knowledge and supplements the observation of an increasing number of zoster-related hospitalisations with age [9]. However, the simulation model is based on an assumption that observed differences in herpes zoster incidences between people living with and without children result solely from external boosting by varicella. Other factors, such as a more healthy lifestyle of adults caring for children, may also play an important role, but the leverage is unknown. A further assumption made by Brisson *et al.* [16] was the elimination of VZV transmission in the population immediately after the start of a vaccination campaign. The authors concede that this leads to an overestimation of the initial increase in the number of herpes zoster cases for countries with a slow increase in routine coverage rates. In the USA, the coverage rate increased from 26% in 1997 to 68% in 2000, while the reduction in reported varicella cases between 1995 and 2000 was from 84% to 71% [10]. A further concern is that the data quality is difficult to assess, because the absolute numbers of cases are not supplied for the denoted incidence estimates. The large confidence interval (CI) for the estimated duration of immunity caused by exter-

nal boosting, i.e., a mean of 20 years (95% CI: 7–41 years) [16], indicates a remarkably high level of uncertainty. Overall, it seems that the simulation results obtained with the model of Brisson *et al*. [16] can be considered as a theoretical worst-case scenario concerning the onset of the possible effect. Furthermore, there is considerable uncertainty with respect to the scope of the effect.

In conclusion, mathematical models cannot substitute for, but can supplement, clinical and epidemiological data in this scenario. They are essential for situations that require long-term prediction of the implications of different vaccination strategies for which empirical data cannot be obtained in advance. The quality and validity of predictions are heavily dependent on solid and valid input data for the baseline time-point and transition rates between pre-specified model compartments. In cases where there is much uncertainty regarding some input parameters, extensive sensitivity analyses are necessary in order to verify the results. In addition, studies should be initiated to examine how much of the reactivation potency of latent VZV can be attributed to wild-type virus spread, and how much is a result of other coexisting factors.

POTENTIAL RISKS OF REACTIVATION FOLLOWING VACCINATION

The possibility of a change in the epidemiology of herpes zoster as a consequence of mass varicella vaccination has long been recognised [6], and surveillance systems have been established to detect changes in herpes zoster incidence. Clinically, there is only one preliminary study [11] that has shown an increased herpes zoster-related hospitalisation rate in the elderly following the introduction of mass varicella vaccination in the USA. However, these were interim results, and the level of vaccine coverage was not provided. In contrast, the studies funded by the Centers for Disease Control in Massachusetts and Seattle have, to date, shown no increase in herpes zoster incidence for any age group at either site [5], which is a finding similar to that of Goldman [13]. Comparison of the herpes zoster incidence rates reported by Goldman [12] with pre-licensing estimates from historical studies or surveys should be interpreted with care, because of possible confounding factors and adjustment for under-reporting. As these are interim data, further results from these investigations are needed for a clearer picture.

For the special case of leukaemic children, two clinical studies [24,25] showed that re-exposure to VZV, either by close contact with varicella or by vaccination, reduced the risk of contracting herpes zoster. However, vaccine virus seems to have less of a tendency to reactivate than wild-type virus, since leukaemic vaccinees were less likely to develop herpes zoster than leukaemic children with a history of varicella [24].

CONCLUSIONS

In summary, knowledge of the exact relationship between varicella and herpes zoster is still remarkably limited, although increasing efforts to understand this relationship have been made recently. This is true for the process and factors influencing reactivation at an individual level, as well as for the epidemiological situation at a population level [7]. Additional and comprehensive clinical data on the association between varicella vaccination and herpes zoster incidence in the elderly are essential.

Empirical data suggest that close contact with varicella reduces reactivation of latent virus. However, females seem to have a slightly increased risk of contracting herpes zoster relative to men, perhaps because of more social contacts with children, and therefore with varicella. The reason for this finding is unclear, and it may be the result of combining different influencing factors [7]. Further studies on the mechanisms of VZV reactivation are required to determine whether and to what extent it is the result of a combination or interaction of several factors [1,9]. In particular, no final conclusion regarding the duration of protection can be reached from the results of studies undertaken so far. Brisson *et al*. [16] estimated that varicella exposure boosted immunity to herpes zoster for an average of 20 years, but with a very large CI, denoting a high degree of uncertainty in the estimation.

Surveillance studies and clinical trials to monitor the potential impact of the ongoing routine varicella vaccination programme are now well underway in the USA. Forthcoming data will allow the detection of changes in herpes zoster incidence. This should allow the timely implementation of any measures necessary to avoid

public health problems, and a vaccination programme could be adapted accordingly [17].

The risk of an increased herpes zoster incidence in the initial period following vaccination exists, but the extent of this risk is unclear. If vaccination of the elderly proves to be effective, an increase can be avoided. A recent trial showed that vaccination of immunocompetent patients aged ≥60 years is safe and immunogenic [26]. Thus, a general vaccination programme with public health advantages could be maintained and supplemented with targeted vaccination or vaccination of the elderly if necessary. The available evidence does not appear to justify withholding varicella vaccination from children.

ACKNOWLEDGEMENTS

This work was supported by a grant from GlaxoSmithKline, Munich, Germany.

REFERENCES

1. Centers for Disease Control. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1996; **45**(RR-11): 1–36.
2. Klose T, Banz K, Wagenpfeil S *et al*. Varicella vaccination in Germany: an analysis with focus on the impact on age-shifts and the elimination of the disease. *Eur J Public Health* 2002; **12**(suppl): 68.
3. Banz K, Wagenpfeil S, Neiss A *et al*. The cost-effectiveness of routine childhood varicella vaccination in Germany. *Vaccine* 2003; **21**: 1256–1267.
4. Panagiotopoulos T, Antoniadou I, Valassi-Adam E. Increase in congenital rubella occurrence after immunization in Greece: retrospective study and systematic review. *BMJ* 1999; **319**: 1462–1467.
5. Gershon A. Varicella vaccination in the USA: an update. In: *Handout for the 7th Meeting of the European Working Group on Varicella*. Warsaw: VZV Research Foundation, 2002; 1–7.
6. Garnett G, Grenfell B. The epidemiology of varicella-zoster virus infections: the influence of varicella on the prevalence of herpes zoster. *Epidemiol Infect* 1992; **108**: 513–528.
7. Thomas S, Hall A. What does epidemiology tell us about risk factors for herpes zoster? *Lancet Infect Dis* 2004; **4**: 26–33.
8. Coplan P, Black S, Rojas C *et al*. Incidence and hospitalization rates of varicella and herpes zoster before varicella vaccine introduction: a baseline assessment of the shifting epidemiology of varicella disease. *Pediatr Infect Dis J* 2001; **20**: 641–645.
9. Lin F, Hadler J. Epidemiology of primary varicella and herpes zoster hospitalizations: the pre-varicella vaccine era. *J Infect Dis* 2000; **181**: 1897–1905.
10. Seward J, Watson B, Peterson C *et al*. Varicella disease after introduction of varicella vaccine in the United States, 1995–2000. *JAMA* 2002; **287**: 606–611.
11. Ray P, Zhang L, Lewis E, Shinefield H, Black S. A comparison of pre and post varicella vaccine licensure hospitalization rates for varicella and herpes zoster. In: Weddle A, ed. *Proceedings of the 3rd International Pediatric Infectious Disease Conference*, Monterey, CA. Alexandria, VA: Paediatric Infectious Diseases Society, 2001; 136.
12. Goldman G. Incidence of herpes zoster among children and adolescents in a community with moderate varicella vaccination coverage. *Vaccine* 2003; **21**: 4243–4245.
13. Goldman G. Varicella susceptibility and incidence of herpes zoster among children and adolescents in a community under active surveillance. *Vaccine* 2003; **21**: 4238–4242.
14. Halloran M, Watelet L, Struchiner C. Epidemiologic effects of vaccines with complex direct effects in an age-structured population. *Math Biosci* 1994; **121**: 193–225.
15. Brisson M, Edmunds W. Economic evaluation of vaccination programs: the impact of herd-immunity. *Med Decis Making* 2003; **23**: 76–82.
16. Brisson M, Gay N, Edmunds W, Andrews N. Exposure to varicella boosts immunity to herpes-zoster: implications for mass vaccination against chickenpox. *Vaccine* 2002; **20**: 2500–2507.
17. Thomas S, Wheeler J, Hall A. Contacts with varicella or with children and protection against herpes zoster in adults: a case-control study. *Lancet* 2002; **360**: 678–682.
18. Brisson M, Edmunds W, Gay N, Law B, De Serres G. Modelling the impact of immunization on the epidemiology of varicella zoster virus. *Epidemiol Infect* 2000; **125**: 651–669.
19. Edmunds W, Brisson M. The effect of vaccination on the epidemiology of varicella zoster virus. *J Infect* 2002; **44**: 211–219.
20. Centers for Disease Control. Varicella. In: *Epidemiology and prevention of vaccine-preventable diseases. The pink book course textbook*, 8th edn. Atlanta, GA: Centers for Disease Control, 2004; 159–175.
21. Seward J, Jumaan A, Galil K, Wharton M. Varicella vaccine and shingles: in reply. *JAMA* 2002; **287**: 2211–2212.
22. Solomon B, Kaporis A, Glass A, Simon S, Baldwin H. Lasting immunity to varicella in doctors study (L.I.V.I.D. study). *J Am Acad Dermatol* 1998; **38**: 763–765.
23. Terada K, Hiraga A, Kawano S, Kataoka N. Incidence of herpes zoster in pediatricians and history of reexposure to varicella-zoster-virus in patients with herpes zoster. *Kansen Zasshi* 1995; **69**: 908–912.
24. LaRussa P, Steinberg S, Gershon A. Varicella vaccine for immunocompromised children: results of collaborative studies in the United States and Canada. *J Infect Dis* 1996; **174**(suppl 3): S320–S323.
25. Gershon A, LaRussa P, Steinberg S, Mervish N, Lo S, Meier P. The protective effect of immunologic boosting against zoster: an analysis in leukemic children who were vaccinated against chickenpox. *J Infect Dis* 1996; **173**: 450–453.
26. Levin M, Smith J, Kaufhold R *et al*. Decline in varicella-zoster virus (VZV)-specific cell-mediated immunity with increasing age and boosting with a high-dose VZV vaccine. *J Infect Dis* 2003; **188**: 1336–1344.